REMARKS

The Office Action sent September, 18, 2008 has been received and reviewed. All claims currently under consideration stand rejected. The claims are to be amended as previously set forth. All amendments and cancellations are made without prejudice or disclaimer. No new matter has been added. Reconsideration is respectfully requested.

Claim rejections - 35 U.S.C. § 112

Claims 3, 6, 12, 15, 17 and 18 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. Applicants have amended the claims, and request that the rejections be withdrawn.

Claim 3 has been amended to depend from claim 4, which now recites

> A human binding molecule antibody able to bind to and stimulate a human OX40 receptor, wherein the binding molecule antibody comprises a heavy chain variable region comprising the variable region of amino acid sequence SEQ ID NO:27, or a sequence that is at least 97% homologous thereto, and wherein the human binding molecule antibody comprises a light chain variable region comprising the variable region of amino acid sequence of SEQ ID NO: 31, or a sequence that is at least 97% homologous thereto.

Thus, the claim 4 antibody comprises a heavy chain variable region derived from the amino acid sequence of the heavy chain (SEQ ID NO: 27) of the antibody SC02-021 and a light chain variable region comprising the variable region derived from the light chain (SEQ ID NO: 31) of the antibody SC02-021, or a sequence that is at least 97% homologous thereto. The heavy chain variable region and the light chain variable regions are derivable from SEQ ID NO: 12 (which is the amino acid sequence of the scFv binding molecule, which comprises the variable region of both the heavy and light chain), and the amino acid sequences of the heavy and light chain, *i.e.*, SEQ ID NO:27 and SEQ ID NO: 31, respectively. The skilled person would certainly be able to derive from the present specification the amino acid sequences of the variable regions of the heavy and light chain. The binding molecule of present claim 4 thus is structurally defined by the variable heavy and light regions, which are responsible for antigen binding, as well as functionally by being capable of binding to and stimulating the OX-40 receptor.

It is submitted that this subject matter fulfills the written description requirement, as the application discloses at least an antibody with the indicated sequences, and in addition thereto further discloses functional variants of the antibodies (*e.g.*, paragraph **[0066]**, and in particular paragraph **[0067]** of US 2006/0281072). Paragraph **[0067]** describes what functional variants are and thus there is written description for these, this paragraph inter alia expressly disclosing that:

> "Alternatively, functional variants can be binding molecules as defined in the invention comprising an amino acid sequence containing substitutions, insertions, deletions or combinations thereof of one or more amino acids sequences of the parent binding molecules."; and
>
> "Preferably, the amino acid sequences of the variable regions, including, but not limited to, framework regions, hypervariable regions, in particular the CDR3 regions, are modified."; and
>
> "Functional variants intended to fall within the scope of the invention have at least about 50% to about 99%, preferably at least about 60% to about 99%, more preferably at least about 70% to about 99%, even more preferably at least about 80% to about 99%, most preferably at least about 90% to about 99%, in particular at least about 95% to about 99%, and in particular at least about 97% to about 99% amino acid sequence homology with the parent binding molecules as defined herein."

Thus, the specification describes molecules as claimed in claim 4, and hence the written description requirement for this subject matter has been met.

Applicants also refer to the "Written Description Training Materials" (http://www.uspto.gov/web/menu/written.pdf). It is submitted that Example 11B (Art-Recognized Structure-Function Correlation Present) applies at least in part to the instant situation, since for antibodies it is well known by the person of ordinary skill that specific domains are critical to activity, *i.e.*, the CDR regions, in particular the heavy chain CDR3 regions, while other domains are much less relevant for activity, *i.e.*, the framework (FR) regions. This is indeed even described in the specification, *e.g.*, in paragraph **[0067]**.

Even if one were, for the sake of argument, to consider that there were no teaching in the instant application which amino acids will vary (which is not the instant situation), analogous to the situation described in the training materials for claim 2 in Example 11B, it is generally known by the skilled person -as well as disclosed in the specification- that the CDR domains are mainly

responsible for binding and thus required for neutralizing activity, and it is known that conservative mutations in these domains in many cases will not have a great impact on functionality of the domains (and indeed the specification contains teaching about conservative mutations in paragraph **[0039]**) and thus of the antibodies.

Applicants see a clear analogy with the situation described for a protein having "activity Y" in the Example 11B of the Written Description Training Materials, wherein it is stated that "Although all conservative amino acid substitutions in these domains will not necessarily result in a protein having activity Y, those of ordinary skill in the art would expect that many of these conservative substitutions would result in a protein having the required activity." This is also to be expected for conservative mutations in the CDR regions of an antibody. The Example continues by stating that "Further, amino acid substitutions outside of the two identified functional domains are unlikely to greatly affect activity Y. Thus a correlation exists between the function of the claimed protein and the structure of the disclosed binding and catalytic domains". Indeed, applicants submit that completely analogous to this example, the skilled person would expect that amino acid substitutions outside the CDRs, *i.e.,* in the FR of the variable domains of an antibody are unlikely to greatly affect the activity of the antibody, and a correlation exists between the function of the claimed antibody and the structure of the disclosed CDR regions. Thus, as with Example 11B of the Written Description Training Materials", applicants submit that based upon applicants' disclosure and the knowledge within the art, those of ordinary skill in the art would conclude that the applicants were in possession of the claimed genus of antibodies. Hence, it submitted that the written description requirement is met for the instant claims.

Applicants respectfully request reconsideration and withdrawal of the rejection

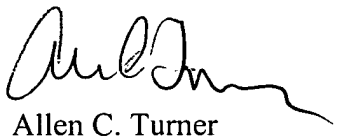
Claims 3, 4, 6, 12, 15, 17-18 and 50 stand rejected under 35 U.S.C. 112, first paragraph, for allegedly not being enabled. Applicants respectfully traverse the rejection.

It is submitted that the skilled person is able to prepare binding molecules as claimed in amended claim 4. Thus, in the specification, in particular Example 7, the construction of fully human immunoglobulin molecules from the selected anti-human OX40 receptor scFV fragments, comprising the heavy and light chain variable regions is described. Thus, primers are described to PCR amplify the heavy and light chain variable regions, in particular primers 5H-B, 3H-B, 5K-G

and 3K-B for SC02-021 (*see, e.g.*, par **[0131]**). In addition, the sequences of the heavy chain and light chain variable regions and the sequence of the CDR3 of the claimed antibodies are now present in the claims. It is submitted that claims, 3, 4, 6, 12, 15, 17-18 and 50 are fully enabled by the specification. Reconsideration and withdrawal of the rejection is respectfully requested.

In light of the foregoing amendments and remarks, the application should be in condition for allowance. If questions remain after consideration of the foregoing, or if the Office should determine that there are additional issues which might be resolved by a telephone conference, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



Allen C. Turner
Registration No. 33,041
Attorney for Applicants
TRASKBRITT, PC
P.O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: 801-532-1922

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